D1305B

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Atlanta District Office
HFI-35

60 8th Street, N.E.
Atlanta, Georgia 30309

November 17, 1997

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Charles H. Heimbold
President and CEO
Bristol-Myers Squibb
345 Park Avenue
New York City, NY 10154

WARNING LETTER

Dear Mr. Heimbold:

An inspection of your drug manufacturing facility located in Morrisville, North Carolina, was conducted between September 25 and October 20, 1997, by Investigator Barbara M. Frazier. Our investigator documented several significant deviations from the Current Good Manufacturing Practice Regulations (GMPs) as set forth in Title 21 of the Code of Federal Regulations (21 CFR), Part 211. These deviations cause your drug product, Excedrin, to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act).

You have failed to establish that the level and methodology of in-process testing currently conducted on product blend, tablet cores, and caplet cores will assure batch uniformity and integrity of your drug product. Control procedures should be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. This is particularly critical in your operation as the release of the product is progressive in nature. For tablets and caplets, certain tests such as [redacted] are performed at the core stage.

You conduct no routine blend assay uniformity testing. The only testing currently performed is on a composited sample taken from each (approx. [redacted]) section of tablet and caplet cores produced. Each section of cores manufactured generally contains portions of at least [redacted] blends but can contain up to [redacted] blend batches. No attempt is made to ensure that the [redacted] core samples will include all blends utilized in the batch. The testing of the batch is based on the [redacted] samples which may not be representative of the blends used. A portion of each of the [redacted] samples is composited and set aside for content uniformity testing. [redacted] tablets or caplets are selected from this composite to test for content uniformity of the batch. These [redacted] samples are selected from composites of up to [redacted] tablets or caplets, further diluting the possibility that

they are representative of the batch or are inclusive of all blends utilized. The results from these [redacted] samples will be used to establish the content uniformity of a section of product comprising approximately [redacted] tablets or caplets.

There were no formalized written procedures specifically describing the handling and compositing of these [redacted] samples at the core stage. These samples are collected by production personnel as each section is pressed. Although these procedures were currently being revised, our investigator was told that specifics had been dropped during some previous revision of the procedures.

Our investigator's review of Incident Investigation Reports revealed instances which exemplified the failure of the current content uniformity sampling practices to be representative of the batch. Initial assay and content uniformity testing on Batch 610927 met specifications. Initial content uniformity results ranged from 96.6 to 104.5%. The batch was subsequently resampled during an investigation into low aspirin results in the previous batch produced on the press. New samples were taken from the beginning and end of the batch. These new samples revealed aspirin content uniformity results from the beginning of the batch averaging 84.8% in section B and 87.9% in section A.

Another similar example was noted in resampling conducted on Batch 706469. [redacted] tablets from each section (A-F) were tested for content uniformity. Initial caffeine results met specifications except for section D. Resampling from the beginning and end of sections C and E revealed failing caffeine results of 74.12 to 85.39% for the end of section C and 70.96 to 104.25% for the beginning of section E.

You failed to conduct an appropriate investigation into caffeine content uniformity problems in batch 605884 which had three results out of thirty which exceeded 115%. The Incident Report did not include any information on testing of the blends used in the batch. The report included no indication that any additional sampling or testing was performed on the prior batch produced on the same press (Batch 605883). Batch records indicated that one of the same blends was used in both batches.

The product validation studies did not provide a high degree of assurance that the blending practices and procedures in use were effective and could consistently produce a product meeting its predetermined specifications and quality attributes. Our investigator reviewed validation protocols for Excedrin Extra Strength tablets (protocol 6124), caplets (protocol 6054), and geltabs (protocol 6055). The protocol listed anticipated results for the unit dose blend samples as means, instead of specific ranges. The protocol also utilized a looser relative standard deviation than is acceptable for release testing of cores. We are concerned that your protocol methodology may conceal true product quality problems.

The protocol for geltabs stated that no unit dose blend samples would be done as content uniformity was validated by protocol 6124. The geltab protocol (6055) was approved on 11/22/96 although quality assurance did not evaluate the 6124 results until 11/25/96 and the

6124 protocol was not approved until 12/5/96. Unit dose sampling of the tablet blend found one acetaminophen result which exceeded 115% in each of two batches. Geltab blend sampling found one batch of blend with 1 acetaminophen and one caffeine result which exceeded 115% and one batch of blend with 3 acetaminophen and one caffeine result which exceeded 115%. The tablet protocol stated that the product and process would be considered acceptable if test results are found to be within the specification outlined in the Anticipated Results of the protocol which included only means. The protocols for caplets and geltabs did not list any anticipated results for content uniformity of blend, although blend samples were taken and tested. Review of blend sample content uniformity validation results found analyses for the caplets and geltabs which exceeded 115%, with no additional sampling or testing being conducted.

The only protocol which specified that unit dose thief sampling of the blend would be collected and tested was the tablet protocol, although blend samples were collected for caplets and geltabs. There was no documentation of the actual amount of blend taken from each location. The amount reportedly taken was [redacted] grams per site but the amount tested was approximately equivalent to the weight of one tablet. This amount of product is approximately [redacted] times the weight of one tablet or caplet. The current practice is to analyze the entire amount sampled. During the 1996 validation, a portion of the blend from each cavity was weighed to approximate the weight of one tablet. You have failed to demonstrate that your sampling technique is representative of all portions and concentrations of the blend. You could provide no justification for the current sampling size in use.

Many of the above deviations were included on the FDA 483 (Inspectional Observations) which was issued to and discussed with Arthur L. Baker, Senior Manager Regulatory Compliance, at the conclusion of the inspection. A copy of the FDA 483 is enclosed for your review. The violations noted in this letter and in the FDA 483 could be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems. The deviations discussed above and included on the FDA 483 should not be construed as an all inclusive list of violations which may be in existence at your firm. It is your responsibility to ensure adherence to each requirement of the Act.

You are responsible for investigating and determining the causes of the violations identified by FDA. You should take immediate actions to correct these violations. Failure to promptly correct these deviations may result in legal sanctions provided by the law such as product seizure and/or injunction, without further notice to you. Federal agencies are advised of the issuance of all warning letters involving drugs so that they may take this information into account when considering the award of contracts.

The current inspection was conducted in conjunction with the review of [redacted]

We are cognizant of the fact that corrective actions have been discussed with Investigator Frazier since the inspection was concluded. We are also in receipt of written responses dated 10/27/97 and 11/11/97 to the FDA 483. We continue to have concerns over the proposed sampling methodology however. A more detailed response with our review findings will be forthcoming.

You should notify this office in writing, within fifteen (15) working days of receipt of this letter, of any additional steps you have taken to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of similar violations. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which corrections will be completed. Your response should be addressed to Philip S. Campbell, Compliance Officer, at the address noted in the letterhead.

Sincerely,

Ballard H. Graham, Director
Atlanta District

Enclosure

cc: Robert J. Crew, Jr.
Bristol Myers Products,Inc.
9707 Chapel Hill Road
Morrisville, NC 27560